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CONSIDERATION OF THE METABOLIC ROLES OF NON-TOXINS IN TOBACCO-SMOKE

As considerable attention is being given to the analysis and filtration of known toxins in tobacco smoke, our thoughts have turned toward compounds which have no easily observed toxic properties but which might, however, be potentially hazardous.

It is difficult to make a clear division between toxins and non-toxins, since virtually all chemicals in sufficiently high concentrations have toxic effects, while none are toxic if their concentration is sufficiently small. At present it is not necessary to make an absolute distinction between the two; a typical classification, as shown below, will suffice to divide, arbitrarily, chemicals into toxins and non-toxins:

- | | |
|--------------------------|-----------------|
| 1. Extremely toxic | 1 mg/kg or less |
| 2. Highly toxic | 1-50 mg/kg |
| 3. Moderately toxic | 50-500 mg/kg |
| 4. Slightly toxic | .5-5 g/kg |
| 5. Practically non-toxic | 5-15 g/kg |
| 6. Relatively harmless | 15 g/kg |

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The concentrations shown above are described as the levels required to produce 'harmful effects'*. For our purposes groups 5 and 6 will be considered as non-toxins.

It is reasonable to assume that the bulk of non-toxic smoke constituents will be metabolised or excreted by the smoker with no ill effects. It is possible, however, that some apparently harmless substances may be metabolised by the body into more toxic products (toxification) and it is also possible that some non-toxic substances may behave as haptens and produce minor localised allergic reactions.

Toxification

Examples of toxification are best drawn from the field of drugs and pesticides. These examples have no direct relevance to human beings or to tobacco smoke and are only intended to draw attention to the principle involved.

* Essentials of Toxicology, T.A. Loomis, Lea & Febiger, Philadelphia 1968.

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The insecticide Malathion is relatively inactive. Insects are equipped with two enzymes systems for dealing with Malathion. The first set, the microsomal enzymes, rapidly oxidise the compound to Malaoxon which is an active insecticide. The second set, the A-esterases, slowly hydrolyse the oxidised form into inactive products. The net result is that Malaoxon is formed faster than the A-esterases can dispose of it and thus exerts a toxic effect on the organism.

The pesticide Parathion behaves similarly. It is enzymatically oxidised to Paraoxon a more active product. A better known example is that of Prontosil, the antibiotic, which is reduced to sulfanilamide a product having toxic and antibacterial properties. The toxic properties are not lethal and the body possesses a mechanism for converting sulfanilamide to acetyl sulfanilamide a non-toxic derivative. The first reaction takes place more rapidly than the second thus permitting temporary accumulations of the antibiotic.

Haptens


The possibility of the existence of haptens in smoke has, as far as we know, received no attention. In drawing attention to this class of compounds it is necessary to provide a little background information. Large molecules (antigens) on introduction into an animal, give rise, after an induction period, to new proteins called antibodies. If the animal is later exposed to more of the antigen a specific antibody/antigen reaction will take place. This reaction is made use of in immunisation against infectious disease and also provides the body's defense mechanism against foreign protein.

Small molecules can achieve much the same effect by reacting with endogenous protein to form an antigen. The small molecule is termed a hapten. Initial exposure of an animal to a hapten may lead to sensitisation of the animal. Exposures to the hapten on subsequent occasions will then lead to formation of the antigen which reacts with the preformed antibody, resulting in cell damage.

To explain why the normal antigens give rise to smooth antibody-antigen reactions while the haptens result in an allergic type reaction, it is postulated that haptens or allergens cause formation of cell bound antibodies. The immune reaction involving cell bound antibodies is thought to result in the liberation of histamine and damage to the cell. Normal antigens stimulate production of serum antibodies which take part in non-disruptive immune reactions.

To perform the function of a hapten the chemical must be able to react covalently with proteins. Compounds with the following functional groups can have this property:

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Thiol	-SH
diazonium	-N ⁺ =N-
sulfonic acid	-SO ₃ H
aldehyde	-CHO
active halogen	
quinone	

A number of these functional groups can be found in smoke components.

Assuming that compounds which undergo metabolic toxification and haptens are represented in smoke, how can they be identified? It is suggested that, to investigate the first class of compounds, information be gathered about the metabolism of non-toxic compounds in smoke, bearing in mind that synergistic effects may occur. To investigate the second class of compounds, information about low molecular weight haptens should be collected to see if any of these do in fact occur in smoke. It is important to find out whether persistent exposure to a hapten results in desensitisation or whether the allergic response continues. If haptens are present in smoke and the allergic reaction persists, it is possible that this type of continuous insult could lead to permanent changes in the lung and might be linked with lung ailments like emphysema.

It is felt that plans for experimental work in this area would be premature and that a broad literature survey should suffice to substantiate or disprove the hypothesis.

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